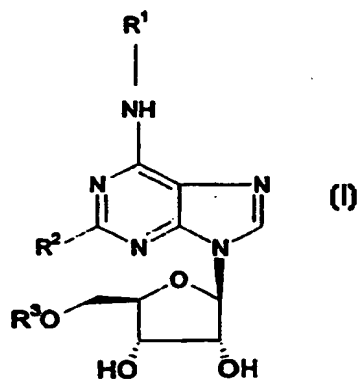




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|--|
| (51) International Patent Classification ⁶ : C07H 19/00 | A2 | (11) International Publication Number: WO 99/24450 (43) International Publication Date: 20 May 1999 (20.05.99) |
| <p>(21) International Application Number: PCT/EP98/07022</p> <p>(22) International Filing Date: 6 November 1998 (06.11.98)</p> <p>(30) Priority Data: 9723566.7 8 November 1997 (08.11.97) GB</p> <p>(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BOX, Philip, Charles [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDKINS, Brian, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PENNELL, Andrew, Michael, Kenneth [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).</p> <p>(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).</p> | | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p> |

(54) Title: CHEMICAL COMPOUNDS



(57) Abstract

A compound of formula (I) wherein R² represents C₁₋₃ alkyl, halogen or hydrogen; R³ represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms; and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof. These compounds are agonists of the Adenosine A₁ receptor.

FOR THE PURPOSES OF INFORMATION ONLY

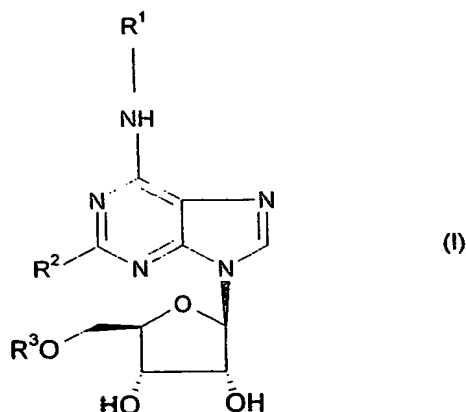
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

CHEMICAL COMPOUNDS

The present invention relates to novel adenosine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Thus the invention provides compounds of formula (I) which are agonists at the adenosine A1 receptor



wherein R^2 represents C_{1-3} alkyl, halogen or hydrogen;

R^3 represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms;

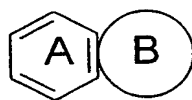
R^1 represents a group selected from

(1) $-(alk)_n-$ (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from OH, halogen, $-(C_{1-3})$ alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S and optionally substituted by one or more substituents selected from the group consisting of $-(C_{1-3})$

₃)alkyl, -CO₂-(C₁₋₄) alkyl, -CO(C₁₋₃alkyl), -S(=O)_n-(C₁₋₃alkyl), -CONR^aR^b (wherein R^a and R^b independently represent H or C₁₋₃alkyl), or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)_n, where n is 1 or 2.

- 5 (3) Straight or branched C₁₋₁₂ alkyl, optionally including one or more O, S(=O)_n (where n is 0, 1 or 2), or N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups; phenyl, halogen, hydroxy or NR^aR^b wherein R^a and R^b both represent C₁₋₃alkyl or hydrogen.
- 10 (4) a fused bicyclic aromatic ring



15 wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted -CO₂-(C₁₋₃alkyl).

- (5) a phenyl group optionally substituted by one or more substituents selected from:
- 20 -halogen, -SO₃H, -(alk)_nOH, -(alk)_n-cyano, -(O)_n-(C₁₋₆) -alkyl (optionally substituted by one or more halogens), -(alk)_n-nitro, -(O)_m-(alk)_n-CO₂R^c, -(alk)_n-CONR^cR^d, -(alk)_n-COR^c, -(alk)_n-SOR^e, -(alk)_n-SO₂R^e, -(alk)_n-SO₂NR^cR^d, -(alk)_n-OR^c, -(alk)_n-(CO)_m-NHSO₂R^e, -(alk)_n-NHCOR^c, -(alk)_n-NR^cR^d wherein m and n are 0 or 1 and alk represents a C₁₋₆alkylene group or C₂₋₆ alkenyl group.
- 25 (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C₁₋₃alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d , R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents C_{1-3} alkyl.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

Conveniently, the adenosine A1 agonists of the general formula (I) above exhibit greater activity at the adenosine A1 receptor than the other adenosine receptor subtypes, particularly A3.

More particularly the compounds exhibit little or no activity at the A3 receptor.

It will be appreciated that wherein R^1 and/or R^2 in compounds of formula (I) contain one or more asymmetric carbon atoms the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. Otherwise the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

As used herein, the term "alkyl" means a straight or branched alkyl group. Examples of suitable alkyl groups within R^1 and R^2 include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl and 2,2-dimethylpropyl.

As used herein, the term "alkylene" means a straight or branched chain alkylene group containing 1 to 6 carbon atoms e.g. methylene.

As used herein, the term " C_{2-6} alkenyl" means a straight or branched chain alkenyl group containing 2 to 6 carbon atoms. Allyl represents an example of a suitable C_{2-6} alkenyl group.

The term "halogen" means fluorine, chlorine, bromine or iodine.

By aliphatic heterocyclic group is meant a cyclic group of 4-6 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen or sulfur. This group may optionally be substituted as defined hereinabove.

5

The term heterocyclic aromatic group refers to an aromatic mono or bicyclic ring system comprising from 5 to 10 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen and sulfur, which ring system may optionally be substituted as defined hereinabove.

10

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. A particularly suitable pharmaceutically acceptable salt of the compounds of formula (I) is the hydrochloride salt. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. The solvates may be, for example, hydrates.

15

20

R^3 preferably represents a C_{1-3} fluoroalkyl group especially a fluoromethyl group. More preferably R^3 represents a trifluoromethyl group.

25

R^2 preferably represents hydrogen, methyl or halogen, more preferably hydrogen, methyl or chlorine.

30

Conveniently, R^1 may represent $(alk)_n-C_{3-6}$ -cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH or is unsubstituted. Preferably, n represents zero. More preferably, the cycloalkyl group is monosubstituted by OH or fluorine. More preferably the cycloalkyl ring has 5 carbon members.

- Alternatively R^1 may represent a substituted or unsubstituted aliphatic heterocyclic group, the substituent being selected from the group consisting of $-(CO_2)$ $-(C_{1-4})$ alkyl $-CO-(C_{1-3})$ alkyl, $-S(=O)_n-(C_{1-3})$ alkyl, $CONR^aR^b$ wherein R^a and R^b are defined herein above, and when there is a heteroatom S in the ring, this heteroatom may optionally be substituted by $(=O)_n$ where n is 0, 1 or 2. More preferably the heterocyclic ring is unsubstituted or the substituents are $-CO_2(C_{1-4})$ alkyl, or when the heteroatom is S, the substituent $(=O)_n$ is attached to the heterocyclic S atom. More preferably, when there is a sulfur heteroatom in the ring this S is unsubstituted.
- Conveniently the aliphatic heterocyclic group is unsubstituted or when the substituent is $-CO_2(C_{1-4})$ alkyl the heteroatom is nitrogen and the substituent is attached directly to said ring nitrogen atom.
- Preferably the heterocyclic ring is 5 or 6 membered and more preferably contains only one O, N or S heteroatom.
- Alternatively, R^1 may represent a straight or branched alkyl of 1-5 carbon atoms optionally with at least one S $(=O)_n$ where n = 0, 1 or 2 and/or N substituted in the chain. Where there is an S $(=O)_n$ in the chain, preferably n is 1 or 2. The alkyl group conveniently may be unsubstituted or substituted by at least one OH group.
- Alternatively R^1 may represent a phenyl group which is substituted by one or more substituents selected from OH and halogen. Preferably the phenyl is disubstituted in the 2,4 positions. Preferably both substituents are halogen more particularly, fluorine and chlorine. For example, a particularly preferred combination is 2-fluoro and 4-chloro.
- It is to be understood that the present invention covers all combinations of particular and preferred groups mentioned above.

Particular compounds according to the invention include:

- N-(Tetrahydro-pyran-4-yl)-5'-O-trifluoromethyl-adenosine,
N-(2-Pyridin-4-yl-ethyl)-5'-O-trifluoromethyl-adenosine,

- N-(2S-Fluoro-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine,
 N-(Tetrahydro-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine,
 N-(3,4-Difluoro-phenyl)-5'-O-trifluoromethyl-adenosine,
 N-(3-Fluoro-phenyl)-5'-O-trifluoromethyl-adenosine,
 5 N-(exo-Bicyclo[2.2.1]hept-2-yl)-5'-O-trifluoromethyl-adenosine,
 N-(1,1-Dioxo-hexahydro-1. δ .6-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine,
 N-tert-Butyl-5'-O-trifluoromethyl-adenosine,
 4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-
 purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,
 10 N-(2S-Hydroxy-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine,
 N-(rel-2,3-Dihydroxy-propyl)-5'-O-trifluoromethyl-adenosine,
 N-(Tetrahydro-furan-3R-yl)-5'-O-trifluoromethyl-adenosine,
 N-(Tetrahydro-furan-3S-yl)-5'-O-trifluoromethyl-adenosine,
 N-{2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-
 15 purin-6-ylamino]-ethyl}-acetamide,
 5'-O-Trifluoromethyl-adenosine,
 2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-
 purin-6-ylamino]-ethanesulfonic acid methylamide,
 4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-2-
 20 methyl-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,
 2-methyl N-(tetrahydro-pyran-4-yl)-5'-O-trifluoromethyl-adenosine,
 5'-O-(3-Fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine,
 2-Chloro-5'-O-(3-fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine,
 N-Cyclopentyl-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
 25 N-(Tetrahydro-pyran-4-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
 N-(2R-Hydroxy-cyclopent-(R)-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
 N-(4-Fluoro-phenyl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine.

30 Compounds according to the invention have applicability as inhibitors of lipolysis
 i.e. they decrease plasma free fatty acid concentrations. The compounds may
 thus be used in the treatment of hyperlipidaemias. Furthermore, as a
 consequence of their anti-lipolytic activity, the compounds have the ability to
 lower elevated blood glucose, insulin and ketone body levels and therefore may
 be of value in the therapy of diabetes. Since anti-lipolytic agents have
 35 hypolipidaemic and hypofibrinogenaemic activity, the compounds may also

show anti-atherosclerotic activity. The anti-lipolytic activity of compounds of the invention has been demonstrated by their ability to lower the concentration of non-esterified fatty acids (NEFA) in starved rats dosed orally according to the method described by P. Strong et al. in Clinical Science (1993), 84, 663-669.

5

In addition to their anti-lipolytic effect, the compounds of the invention may independently affect cardiac function by reducing heart rate and conduction. The compounds may thus be used in the therapy of a number of cardiovascular disorders, for example cardiac arrhythmias, particularly following myocardial infarction, and angina.

10

Furthermore, the compounds of the invention are useful as cardioprotective agents, having applicability in the treatment of ischaemic heart disease. As used herein the term "ischaemic heart disease" includes damage associated with both myocardial ischaemia and reperfusion, for example, associated with coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), cardioplegia, acute myocardial infarction, thrombolysis, stable and unstable angina and cardiac surgery including in particular cardiac transplantation. The compounds of the invention additionally are useful for treating ischaemic damage to other organs. The compounds of the invention may also be valuable in the treatment of other disorders arising as a result of widespread atheromatous disease, for example, peripheral vascular disease (PVD) and stroke.

15

20

25

The compounds may also inhibit renin release and thus be of use in the therapy of hypertension and heart failure. The compounds may also be useful as CNS agents (e.g. as hypnotics, sedatives, analgestics and/or anti-convulsants particularly finding use in the treatment of epilepsy).

30

In addition, the compounds of the invention may find use in the treatment of sleep apnoea.

35

The compound of formula (I) and pharmaceutically acceptable acid addition salts thereof are useful as analgesics. They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically

of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the compound of formula (I) and its pharmaceutically acceptable acid addition salts may be used as a preemptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, diabetic neuropathies associated with diabetes, trigeminal neuralgia, pain associated with functional bowel disorders, e.g. irritable bowel syndrome, non cardiac chest pain and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The compound of formula (I) may also be used in the treatment or prevention of pain associated with migraine, tension headache and cluster headaches, pain associated with functional bowel disorders (e.g. IBS), non cardiac chest pain and non ulcer dyspepsia.

Accordingly, the invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or whereby the therapy involves the treatment of ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering from a CNS disorder, sleep apnoea or pain.

In a further aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering a CNS disorder or suffering from sleep apnoea or suffering pain, which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In respect of the above mentioned ischaemic treatment, it has been found that according to a particularly unexpected aspect of the present invention, not only does administration of a compound of formula (I) prior to ischaemia provide

protection against myocardial infarction, but protection is also afforded if the compound of formula (I) is administered after the ischaemic event and before reperfusion. This means that the methods of the present invention are applicable not only where ischaemia is planned or expected, for example in cardiac surgery, but also in cases of sudden or unexpected ischaemia, for example in heart attack and unstable angina.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

In yet a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in association with a pharmaceutical carrier and/or excipient.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in association with a pharmaceutical carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering from a CNS disorder, sleep apnoea or pain.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier and/or excipient.

Compositions according to the invention may be formulated for topical, oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The compositions may be adapted for sustained release.

For topical administration, the pharmaceutical composition may be given in the form of a transdermal patch.

5 Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycolate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated
10 according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup,
15 methyl cellulose, or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents (e.g. mannitol)
20 as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

25 The compounds of formula (I) may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as
30 suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

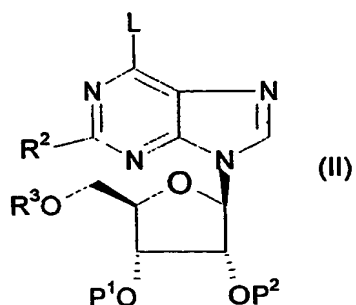
- 5 A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 1mg to 2g, preferably 1mg to 100mg, of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient.
- 10 The dosage will also depend on the route of administration.

- In a yet further aspect the invention also provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of human or animal subjects
- 15 suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease (PVD) or stroke, or which patient is suffering from a CNS disorder, sleep apnoea or pain.

- 20 The compounds of formula (I) and physiologically acceptable salts or solvates thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups R^1 , R^2 and R^3 are as defined for compounds of formula
- 25 (I) unless otherwise stated.

According to a first general process (A), a compound of formula (I) may be prepared by reacting a compound of formula (II).

12

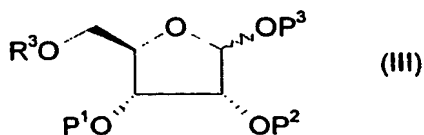


wherein, L represents a leaving group such as a halogen atom (e.g. a chlorine atom) and P¹ and P² represent hydrogen or a suitable protecting group (e.g. acetyl) with a compound of formula R¹NH₂ or a salt thereof, under basic conditions.

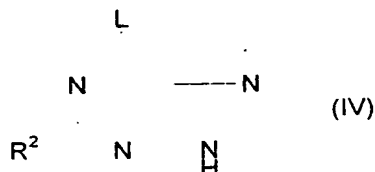
Compounds of formula (II) may be used to produce compounds of formula (I) directly by reaction with the group R¹NH₂ either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g. dimethylformamide), a halogenated hydrocarbon (e.g. chloroform) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine.

This reaction may be preceded or followed where appropriate by in situ removal of the P¹ and P² protecting groups. For example when P¹ and P² represent acetyl, this may be effected with an amine such as ammonia or tert butylamine in a solvent such as methanol at a convenient temperature.

Compounds of formula (II) may be prepared by the reaction of a compound of formula (III).



wherein P^3 represents a suitable protecting group for example C_{1-3} alkyl or acetyl, and P^1 , P^2 and R^3 are as defined above, with a compound of formula (IV)



wherein L and R^2 are as defined above.

5

The reaction is conveniently carried out in a suitable solvent, such as acetonitrile in the presence of a silylating agent such as trimethylsilyl trifluoromethane sulfonate and a base such as diazabicyclo [5.4.0]undec-7-ene (DBU). Alternatively the compound of formula (IV) may first be silylated with a suitable

10 silylating agent, for example, hexamethyldisilazane reaction of the silylated intermediate with a compound of formula (III) and followed by a suitable Lewis acid, e.g. trimethylsilyl trifluoromethanesulfonate in a suitable solvent such as acetonitrile.

15

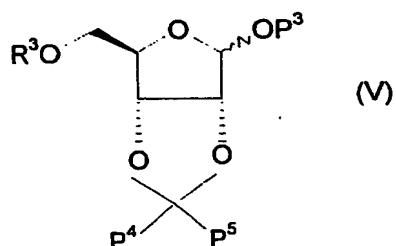
Compounds of formula (IV) are either known in the art or may be prepared from known compounds using methods analogous to those used to prepare the known compounds of formula (IV).

20

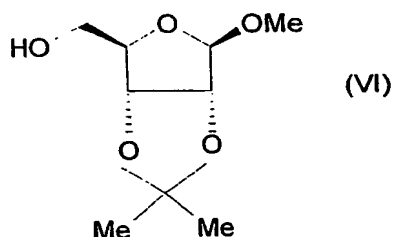
Compounds of formula (III) may be prepared from alternative protected compounds by replacement of the alternate protecting groups with P^1 and P^2 ; for example when P^1 and P^2 represent acetyl, compounds of formula (III) may be prepared from compounds of formula (V) wherein P^4 and P^5 represent C_{1-3} alkyl and P^3 is as defined above, by acid catalysed removal of the alkylidene protecting group, e.g. with hydrogen chloride in methanol, followed by in situ

25 acylation for example with acetic anhydride in the presence of a base such as pyridine, in a solvent such as dichloromethane.

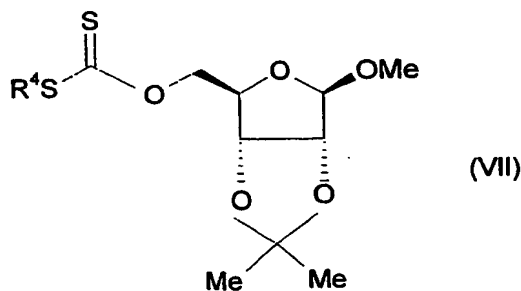
14



Compounds of formula (V) are known compounds or prepared by methods analagous to those used in the art to prepare the known compounds of formula (V). For example compounds of formula (V) wherein P³, P⁴ and P⁵ represent methyl and R³ represents CF₃ may be prepared from the known compound (VI) shown below



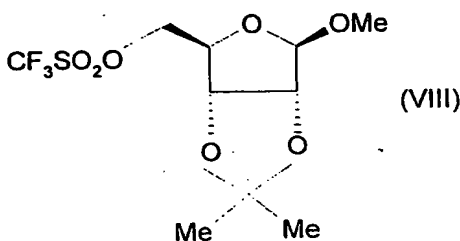
by reacting (VI) with a suitable base, e.g. sodium hydride followed by carbon disulphide together with an alkylating agent R⁴L where L is a leaving group such as halogen (e.g. a bromine or iodine atom) and R⁴ is an alkyl group as previously defined, for example, methyl iodide to produce the compound (VII).



Compound (VII) maybe treated with a suitable brominating agent, e.g. dibromomethylhydrantoin, and a pyridine/hydrogen fluoride complex in a suitable solvent such as dichloromethane according to the method of Hiyouma T.

et. al., Tetrahedron Letters 1992, 4173-4176 to produce the compound of formula (V).

5 Alternatively the known compound (VIII) shown below can be reacted with tris(dimethylamino) sulfur trifluoromethoxide in a suitable solvent such as dichloromethane



10

to produce the compound of formula (V).

15

It will be appreciated by a skilled person that the acetyl group in any of the compounds above could be replaced with any suitable protecting group, for example, other esters.

20

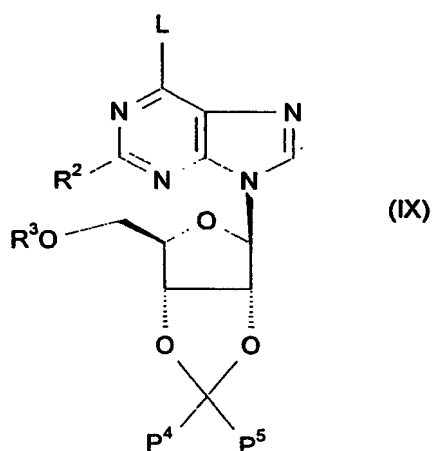
By analogous methods, compounds of formula (I) or (II) may also be prepared from compounds wherein alkylidene groups defined by P⁴ and P⁵ replace P¹ and P². This reaction represents an exchange of one protecting group for another and such reactions will be apparent to a person skilled in the art.

25

A further process (B) comprises converting a compound of formula (I) into a different compound of formula (I) by modifying the R¹, R² or R³ group therein.

Compounds of formula (II) may also conveniently be prepared by the removal of the alkylidene protecting group from a compound of formula (IX)

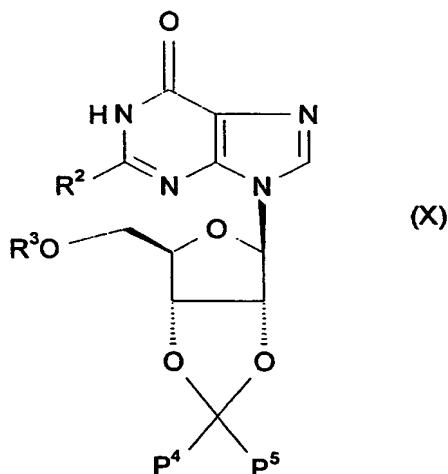
16



wherein P^4 , P^5 , R^3 , R^2 and L are as defined previously under the conditions described hereinabove.

5

Compounds of formula (IX) may be prepared by treating a compound of formula (X)



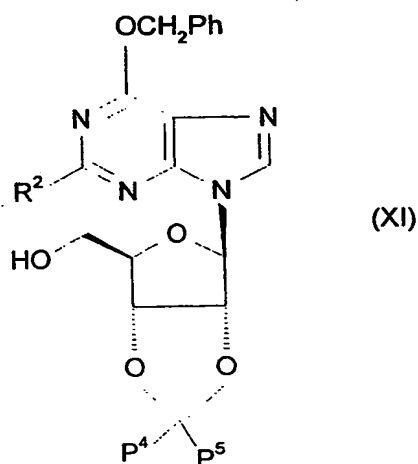
10

wherein P^4 and P^5 are as defined previously with a halogenating (e.g. chlorinating) agent under conventional conditions. Thus, for example, chlorination may conveniently be effected by treating (X) with phosphorus oxychloride in the presence of an organic base such as 4-dimethylaminopyridine and in a suitable solvent such as acetonitrile at an elevated temperature (e.g. up to the reflux temperature of the solvent).

15

17

Compounds of formula (X) may be prepared from compounds of formula (XI)

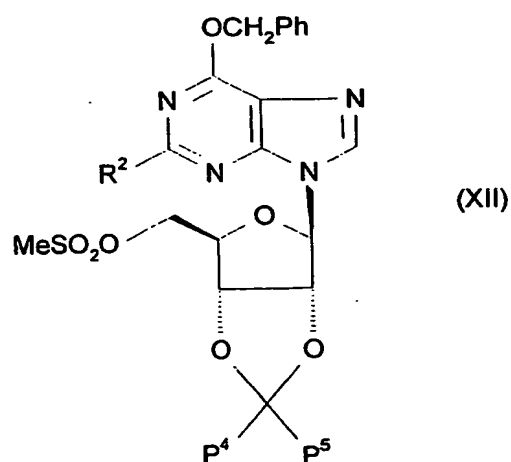


5

by reaction with hydrogen or a source of hydrogen such as ammonium formate in the presence of a suitable catalyst such as palladium or carbon in a suitable solvent such as ethanol.

10

Compounds of formula (XI) may be prepared from compounds of formula (XII).

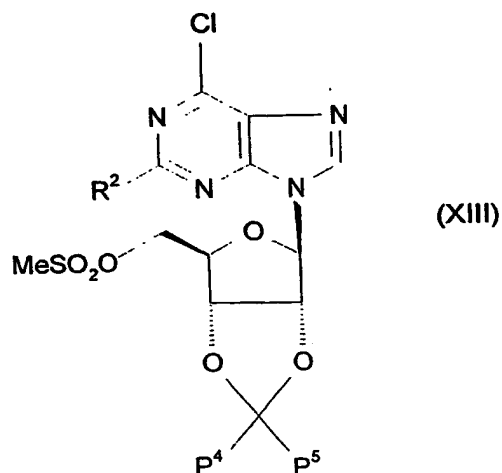


by reaction with an alcohol R^3OH in the presence of a strong base such as sodium hydride in a suitable inert solvent such as dimethylformamide.

15

Compounds of formula (XII) may be prepared from compounds of formula (XIII)

18

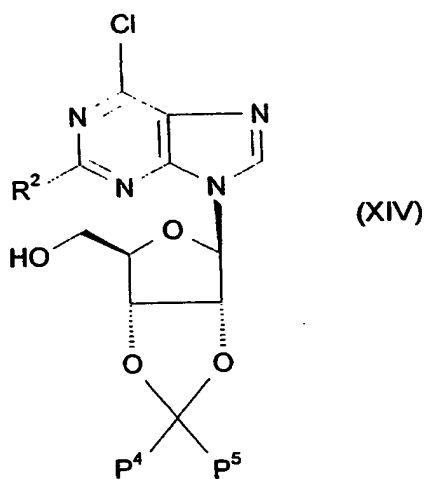


by reacting with benzyl alcohol in the presence of a suitable strong base such as sodium hydride in an inert solvent such as tetrahydrofuran.

5

Compounds of formula (XIII) may be prepared from compounds of formula (XIV) by reaction with methane sulfonyl chloride in the presence of a suitable base such as triethylamine, diisopropylethylamine or pyridine in a suitable solvent such as dichloromethane.

10



It will be appreciated that R^1 or R^2 or R^3 may be converted into a different R^1 , or R^2 or R^3 grouping as an intermediate step in the overall synthesis of

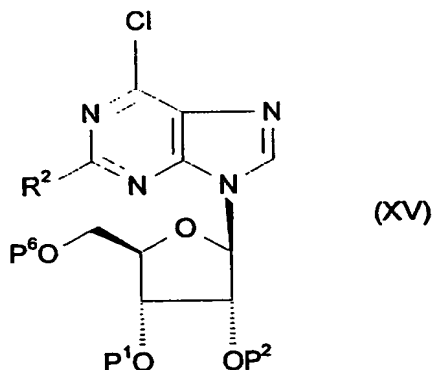
compounds of the invention whereas process (B) hereinabove merely describes interconversion as a final step process.

Compounds of formula (XIV) are either known in the art or may be prepared from known compounds using methods analogous to those used in the art to prepare the known compounds of formula (XIV).

Certain compounds of formulae (II), (III) and (V) are novel intermediates and form a further aspect of the present invention.

Compounds of the formula R^1NH_2 are either known compounds or may be prepared from known compounds using conventional procedures with some exceptions indicated in the experimental section hereinbelow.

In an alternative process (C) compounds of formula (I) may be prepared from compounds of formula (XV).

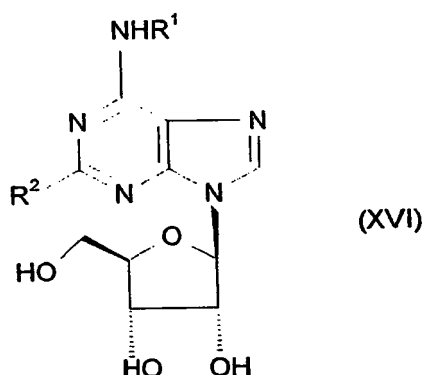


wherein P^1 and P^2 are suitable protecting groups as defined above and P^6 also represents a suitable protecting group. For example when R^2 represents Cl, conveniently P^1 , P^2 and P^6 all represent benzoyl (this is a known compound).

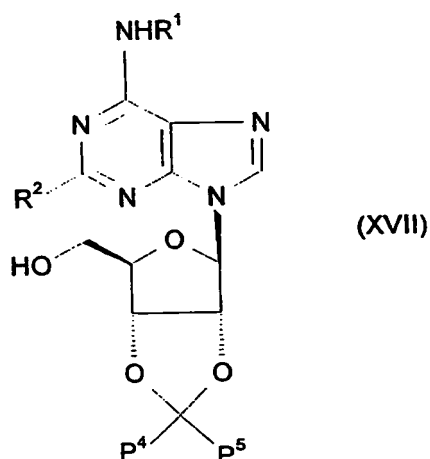
Compounds of formula (XV) may be used to produce compounds of formula (I) by reaction with the group R^1NH_2 either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g.

dimethylformamide), a halogenated hydrocarbon (e.g. chloroform) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine.

This reaction may be preceded or followed where appropriate by in situ removal of the P^1 , P^2 and P^6 protecting groups. For example when P^1 , P^2 and P^6 represent benzoyl, this may be effected with a carbonate such as potassium carbonate in a solvent such as methanol to form a compound of formula (XVI).



By reacting a compound of (XVI) with protecting groups P^4 and P^5 as defined above a compound of formula (XVII) may be formed.



The R³ group may then be introduced into the compound in methods apparent to those skilled in the art followed by deprotection of the compound as described in Process A above.

5 Specific optical isomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or where appropriate by separation of a mixture of isomers of a compound of formula (I) by conventional means e.g. by fractional crystallisation or
10 chromatography.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently into the form of a pharmaceutically acceptable salt. Where desired, such salts may be converted into the
15 corresponding free bases using conventional methods.

Pharmaceutically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) with an appropriate acid in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol (e.g. methanol, ethanol or isopropanol).
20 Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts of the compounds
25 of formula (I), using conventional methods.

The invention is further illustrated by the following non-limiting Intermediates and Examples.

30 Standard HPLC conditions are as follows:

Standard Automated Preparative HPLC column, conditions & eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco ABZ+ 5µm 100mmx22mm i.d. column
35

eluted with a mixture of solvents consisting of i) 0.1% formic acid in water and ii) 0.05% formic acid in acetonitrile, the eluant being expressed as the percentage of ii) in the solvent mixture, at a flow rate of 4ml per minute. Unless otherwise stated the eluent was used as a gradient of 0-95 % (ii) over 20 minutes.

5

LC/MS System

This system used an ABZ+PLUS, 3.3cm x 4.6mm i.d. column, eluting with solvents: A - 0.1%v/v formic acid + 0.077%w/v ammonium acetate in water; and
10 B - 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1ml per minute. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 - 100% B over 3.5mins; hold at 100% B for 3.5mins; return to 100% A over 0.3mins. The system used a micromass 'platform' spectrometer, with electrospray ionisation mode, positive and negative ion
15 switching, mass range 80-1000 a.m.u.

HPLC System

20 The analytical HPLC system used an inertsil ODS2 150mm x 4.6mm i.d. column, eluting with solvents: A - 0.1%v/v phosphoric acid in water and B - 95:5 acetonitrile:water + 0.1%v/v phosphoric acid. The following gradient protocol was used with a flow rate of 1.0 mL/min: 100% A for 2 min; A+B mixtures, gradient profile 0 - 100% B over 40min; hold at 100% B for 10min.

25

Flash chromatography was carried out over Merck silica gel (Merck 9385) , or Merck alumina (Merck 1077).

Intermediate 1

Dithiocarbonic acid O-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl) ester S-methyl ester

[6R-methoxy-2,2-dimethyl-tetrahydro-(3aR, 6aR)-furo-[3,4-d][1,3]dioxol-4R-yl]-methanol (5.20g) was dissolved in dry THF (70ml) and treated portionwise over 10 min with 60% sodium hydride in oil (1.20g) under nitrogen at 22°C. After 20 min, carbon disulphide (5ml, 6.33g) was added, and the mixture stirred for a further 20 min at 22°C. Iodomethane (2ml) was added and after a further 0.5h at 22°C, the solvent was removed *in vacuo* and the residue treated with water (80ml) and extracted with ethyl acetate. The combined ethyl acetate extracts were dried (Na₂SO₄) and evaporated *in vacuo* to afford the product as a pale yellow oil (8.60g).

TLC SiO₂ (cyclohexane-ether 1:1) R_f = 0.62.

Intermediate 2

(3aR,4R,6R,6aR)-4-Methoxy-2,2-dimethyl-6-trifluoromethoxymethyl-tetrahydro-furo[3,4-d][1,3]dioxole

1,3-Dibromo-5,5-dimethylhydantoin (4.29g) was suspended in dichloromethane (20ml) and hydrogen fluoride-pyridine complex (10ml, ca 80 eq.) added. The mixture was cooled to -70°C under nitrogen and a solution of dithiocarbonic acid O-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl) ester S-methyl ester (1.472g) in dichloromethane (10ml) added. The mixture was then stirred at 0-5°C for 1h before being quenched by slow addition to a mixture of 2M sodium carbonate (250ml) containing sodium metabisulphite (10g). Dichloromethane (60ml) was added and the aqueous layer further extracted with dichloromethane (100ml). The combined dichloromethane extracts were washed with 5% sodium metabisulphite solution, 2M sodium carbonate solution, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography over silica (150g) eluting with cyclohexane-ether (4:1-2:1) to give the title compound as a clear oil (650mg). TLC SiO₂ (cyclohexane-ether 1:1) R_f = 0.5

Intermediate 2 (alternative route)

Trifluoro-methanesulfonic acid 6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl ester (1g) was dissolved in dichloromethane (20ml) and treated with tris(dimethylamino)sulfonium trifluoromethoxide (1.12g), and stirred at 22°C for 16h under nitrogen. The solution was evaporated *in vacuo* and the residue purified by flash chromatography over silica (25g) eluting with cyclohexane-ether (4:1) to afford the title compound as a clear oil (237mg).

Intermediate 3

Acetic acid 2R,4R-diacetoxy-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (α anomer) and acetic acid 2S,4R-diacetoxy-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (β anomer)
(3aR,4R,6R,6aR)-4-Methoxy-2,2-dimethyl-6-trifluoromethoxymethyl-tetrahydro-furo[3,4-d][1,3]dioxole (0.61g) was dissolved in a 9:1 mixture of trifluoroacetic acid-water (10ml) and allowed to stand for 1h at 22°. The solvent was removed *in vacuo* and the residue co-evaporated with toluene. The residue was dissolved in dichloromethane (15ml)-pyridine (5ml) and 4-dimethylaminopyridine (5mg) and acetic anhydride (3ml) added and the solution allowed to stand at 22°C for 17h. The mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (150ml), washed with 2M hydrochloric acid, and 8% sodium bicarbonate, dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography over silica (30g) eluting with cyclohexane-ether (3:1-1:1) gave firstly acetic acid 2S,4R-diacetoxy-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (β anomer) (237mg), followed by acetic acid 2R,4R-diacetoxy-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (α anomer) (202mg).
(β anomer) mass spectrum m/z 362 (MNH_4^+)
(α anomer) mass spectrum m/z 362 (MNH_4^+)

Intermediate 4

Acetic acid 4R-acetoxy-5R-methoxy-2R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester
(3aR,4R,6R,6aR)-4-Methoxy-2,2-dimethyl-6-trifluoromethoxymethyl-tetrahydro-furo[3,4-d][1,3]dioxole (6.67g) was dissolved in methanol (100ml) and treated with conc. hydrochloric acid (3.0ml) and heated under reflux for 65h. After 24 and 48h, 20ml methanol was distilled off and fresh methanol (20ml) added to the

reaction mixture. The solution was evaporated *in vacuo* and the residue co-evaporated with pyridine (10ml), and the residue dissolved in dichloromethane (150ml)-pyridine (15ml). 4-Dimethylaminopyridine (ca. 20mg) and acetic anhydride (9ml) were added and the solution allowed to stand for 24h at 22°C.

5 The solvents were removed *in vacuo* and the residue treated with 8% sodium bicarbonate (150ml), and extracted with ethyl acetate (2x150ml). The organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* and the residue purified by flash chromatography over silica (300g) eluting with cyclohexane-ether (2:1-1:1) to give the title compound (2.45g) as a colourless oil.

10 TLC SiO₂ (ether) R_f = 0.72.

Intermediate 5

Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester

15 6-Chloropurine (0.770g), 1,1,1,3,3,3-hexamethyldisilazane (4ml, 18.96mmol) and toluene (10ml) were heated under reflux under nitrogen for 3h. The solvent was removed *in vacuo* and the residue co-evaporated with toluene (10ml). The residue was taken into dry acetonitrile (12ml) and treated with acetic acid 2S,4R-diacetoxy-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (425mg), 1,8-diazabicycloundec-7-ene (0.28ml) and trimethylsilyl trifluoromethanesulfonate (0.41ml) and stirred at 22°C for 20h under nitrogen, then heated under reflux for 2h. The resulting orange solution was cooled to 20°, poured into 8% sodium bicarbonate solution (100ml) and extracted with ethyl acetate. The organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* and the residue purified

20 by flash chromatography over silica (60g) eluting with cyclohexane-ether (1:1-1:4 gradient) to afford the title compound (345mg).

25 TLC SiO₂ (Et₂O) R_f = 0.6.

Intermediate 5 (alternative route)

30 6-Chloropurine (0.31g), 1,1,1,3,3,3-hexamethyldisilazane (2ml) and toluene (6ml) were heated under reflux under nitrogen for 2h. The solvent was removed *in vacuo* and the residue co-evaporated with dry toluene. The solid residue was dissolved in dry acetonitrile (12ml) and acetic acid 4R-acetoxy-5R-methoxy-2R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (0.29g), 1,8-diazabicycloundec-7-ene (0.24ml), and trimethylsilyl trifluoromethanesulfonate

35

(0.35ml) added and the solution heated under reflux under nitrogen for 2h, cooled, and allowed to stand for 17h at 22°C. Further trimethylsilyl trifluoromethanesulfonate (0.35ml) was added, and the solution heated under reflux under nitrogen for a further 5h. The solution was added to 8% sodium bicarbonate (30ml) and extracted with dichloromethane. The organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* to a dark oil, which was purified by flash chromatography over silica (25g) eluting with cyclohexane-ether (1:1-1:4) gave the title compound (304mg).

Mass spectrum *m/z* = 439/441 (MH⁺)

Intermediate 6

(2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-trifluoromethoxymethyl-tetrahydro-furan-3,4-diol

Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (345mg) was dissolved in methanol (6ml), cooled to 0-5°C, and tert-butylamine (0.25ml) added. The solution was allowed to stand at 0-5°C for 1h, then evaporated to dryness *in vacuo*, to afford the title compound as a colourless foam (265mg).

TLC SiO₂ (CH₂Cl₂-MeOH 9:1) R_f = 0.31

Intermediate 7

Acetic acid 4R-acetoxy-2R-(6-chloro-2-methyl-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester

6-Chloro-2-methylpurine hydrochloride (0.734g), 1,1,1,3,3,3-hexamethyl-disilazide (7ml) and dry toluene (20ml) were heated under reflux under nitrogen for 1.5h. The mixture was evaporated *in vacuo* and the residue co-evaporated with toluene then dissolved in dry acetonitrile (15ml). Acetic acid 4R-acetoxy-5R-methoxy-2R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (0.566g), 1,8-diazabicycloundec-7-ene (0.48ml) and trimethylsilyl trifluoromethanesulfonate (1.03ml) were added, and the mixture stirred at 22°C for 10 min then heated under reflux under nitrogen for 2h. Further trimethylsilyl trifluoromethanesulfonate (0.7ml) was added and the solution heated under reflux under nitrogen for a further 1.5h. The dark mixture was added to 8% sodium bicarbonate solution (100ml) and extracted with ethyl acetate. The

organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* and the residue purified by flash chromatography over silica (60g) eluting with ether eluant to afford the product (290mg)
TLC SiO_2 (Et_2O) $R_f = 0.17$.

5

Intermediate 82-(2S-Hydroxy-(S)-cyclopentyl)-isoindole-1,3-dione

(1S,2S)-2-Amino-cyclopentanol hydrochloride (1.20g) was dissolved in a solution of sodium methoxide (497mg) in methanol (10ml), filtered and
10 evaporated *in vacuo*. The residue was dissolved in toluene (30ml) and phthalic anhydride (1.55g) added, and the mixture heated under reflux for 24h. After cooling, ethyl acetate was added and the mixture filtered. The filtrate was evaporated *in vacuo* and the residue purified by flash chromatography over silica (40g) eluting with cyclohexane-ethyl acetate (2:1) to afford the title
15 compound as a colourless solid (1.08g).

Mass spectrum m/z 232 (MH^+)

Intermediate 92-(2S-Fluoro-(S)-cyclopentyl)-isoindole-1,3-dione

20 2-(2S-Hydroxy-(S)-cyclopentyl)-isoindole-1,3-dione (3.42g) was dissolved in dry dichloromethane (55ml) and diethylaminosulfur trifluoride (3.43ml) added, and the solution stirred under reflux under nitrogen for 72h. The solution was poured carefully into 8% sodium bicarbonate solution (100ml) and the organic phase separated. The aqueous phase was further extracted with dichloromethane and
25 the combined organic layers dried (MgSO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography over silica (100g) eluting with cyclohexane-ethyl acetate (1:1) to give the title compound as a cream powder (1.25g).

Mass spec m/z 234 (MH^+), 251 (MNH_4^+)

30

Intermediate 10(1S,2S)-2-Fluorocyclopentylamine hydrochloride

2-(2S-Fluoro-(S)-cyclopentyl)-isoindol-1,3-dione (6.75g), hydrazine hydrate (1.55ml) and ethanol (200ml) were treated with water (1.55ml) and heated under
35 reflux for 4h. The mixture was cooled to 20°C , filtered and the filtrate treated

with conc. hydrochloric acid to pH1. The solution was evaporated *in vacuo* and taken up in water, filtered, and the filtrate evaporated *in vacuo*. The residue was recrystallised (with hot filtration) from ethyl acetate-methanol (3:1) to afford the title compound as an off-white solid (2.59g).

5 NMR δ (DMSO) 8.3 (3H, brs, $-\text{NH}_3^+$), 5.04, (1H, dm, CH_F , J $F-C-H$, 52Hz), 3.49 (1H, brdm, CH , J $F-C-C-H$ 20Hz), and 2.2-1.4 (6Hm, $3 \times \text{CH}_2$).

Intermediate 11

10 [6R-(6-Cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-methanol

A solution of {2,2-dimethyl-6R-[6-chloro-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (3g) in cyclopentylamine (50ml) was heated under reflux for 8h. The solution was cooled to room temperature, concentrated *in vacuo* and the residue applied to a silica gel column (250g) and

15 eluted with ethyl acetate:methanol (20:1) to afford the title compound as a yellow foam (3.87g).

NMR δ (DMSO) 8.4 (1H, s, $-\text{CH}$), 8.26, (1H, brs, CH), 7.85 (1H, brs, NH), 6.19 (1Hd, CH), 5.4 (1Hdd, CH), 5.37 (1H brs, OH), 5.03 (1Hdd CH), 4.57 (1H brs, CH), 4.28 (1Hm, CH), 3.60 (2Hm, CH_2), 1.99 (2Hm, CH_2), 1.8-1.55 (9H, $3 \times \text{CH}_2$ + CH_3), and 1.38 (3Hs, CH_3).

20

Intermediate 12

Cyclopentyl-{9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-amine

25 A solution of [6R-(6-cyclopentylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-methanol (230mg) in tetrahydrofuran (5ml) under nitrogen at 0°C was treated with tri-n-butyl phosphine (0.23ml, 186mg) and 2,2,2-trifluoroethanol (0.07ml, 92mg) followed by 1,1'-azadicarbonyldipiperidine (232mg). The mixture was stirred at 0° for 10 min

30 then allowed to warm to 22°C for 18h. The mixture was then heated to 50°C for 24h, cooled to 22°C, and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography over silica (20g). Elution with ethyl acetate afforded the title compound as a straw coloured foam (110mg).

TLC Silica (ethyl acetate) R_f = 0.45.

Intermediate 13

{2,2-Dimethyl-6R-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol

5 A solution of {2,2-dimethyl-6R-[6-chloro-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (2.00g), tetrahydro-pyran-4-ylamine hydrochloride (926mg) and diisopropylethylamine (2.67ml) in propan-2-ol (15ml) was heated under reflux under nitrogen for 24h and left to cool to room temperature. The amber solution was concentrated under vacuum to give a brown oil which was purified by flash chromatography over silica (115g) with ethyl acetate:methanol (195:5) eluant. This afforded the title compound as a white foam (2.2g).

10 TLC SiO₂ (Methanol:ethyl acetate 5:195), R_f = 0.30.

Intermediate 14

15 {9-[2,2-Dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine

A solution of {2,2-dimethyl-6R-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (400mg) in tetrahydrofuran (10ml) under nitrogen at 0°C was treated with tri-n-butylphosphine (0.38ml, 310mg) and 2,2,2-trifluoroethanol (0.11ml, 153mg) followed by 1,1'-azadipicarbonyldipiperidine (387mg) and the mixture stirred at 0°C for 10 min. The mixture was then stirred at 22°C for 1h then at 50°C for 18h. The mixture was cooled to 22°C and the solvent evaporated *in vacuo*. The residue was purified by chromatography over silica (30g). Elution with methanol:dichloromethane 0.35:10 gave a straw coloured oil. The oil was further purified by chromatography on alumina (20g). Elution with ethyl acetate:cyclohexane (7:3) gave the title compound as a white foam (113mg).

25 TLC SiO₂ (CH₂Cl₂-MeOH 200:7) R_f = 0.31

Intermediate 15

30 Methanesulfonic acid 6R-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl ester

A solution of {2,2-dimethyl-6R-[6-chloro-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (500mg) in dichloromethane (20ml) under nitrogen at 0° was treated with triethylamine (0.32ml, 232mg) and

35

methanesulfonyl chloride (0.15ml) and the mixture was stirred at 0°C for 0.5h. The mixture was poured into 8% sodium bicarbonate solution (20ml) and the organic phase separated, dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a white foam (577mg).

5 TLC Silica ethyl acetate R_f = 0.43.

Intermediate 16

Methanesulfonic acid 6R-(6-benzyloxy-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl ester

10 A solution of benzyl alcohol (1.60ml, 1.675g) in tetrahydrofuran (100ml) under nitrogen at 0°C was treated portionwise with sodium hydride (626mg, 60% in oil) and stirred at 0°C for 0.5h. A solution of methanesulfonic acid 6R-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl ester (5.70g) in tetrahydrofuran (100ml) was added and the mixture was stirred

15 at 0°C for 2h then 22°C for 3 days. Phosphate buffer (pH6.5, 100ml) and water (100ml) were added and the mixture was extracted with ethyl acetate. The combined extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give the title compound as a straw coloured viscous gum (6.67g).

TLC SiO₂ (ethyl acetate:cyclohexane 7:3) R_f = 0.35

20

Intermediate 17

6-Benzyloxy-9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine

2,2,2-Trifluoroethanol (1.13ml, 1.549g) in DMF (dimethyl formamide) (50ml)

25 under nitrogen was treated with sodium hydride (563mg, 60% in oil) and stirred for 0.5h at 22°C. A solution of methanesulfonic acid 6R-(6-benzyloxy-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethyl ester (6.67g) in DMF (50ml) was added and the mixture stirred at 22°C for 18h. Phosphate buffer (pH6.5, 100ml) and water (300ml) were added and the mixture

30 was extracted with ethyl acetate. The combined extracts were washed with water, brine and dried (Na₂SO₄). Evaporation *in vacuo* gave a residue which was purified by flash chromatography over silica (100g). Elution with ethyl acetate:cyclohexane (1:3 then 1:2) gave the title compound as a colourless oil (1.30g).

35 TLC Silica (ethyl acetate:cyclohexane 2:3) R_f = 0.27

Intermediate 18

9-[2,2-Dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-1,9-dihydro-purin-6-one

- 5 A solution of 6-benzyloxy-9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine (1.50g) in ethanol (30ml) was hydrogenated over 10% palladium on carbon (containing 50% water) (350mg). After 35 minutes the mixture was filtered through hyflo and washed carefully with methanol. The filtrate and washings were combined and
10 evaporated *in vacuo* to give the title compound as a white solid (633mg).
Mass spectrum *m/z* 391 (MH⁺)

Intermediate 19

- 15 6-Chloro-9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine

- Phosphorous oxychloride (0.44ml, 726mg) was added to a stirred solution of 9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-1,9-dihydro-purin-6-one (616mg) and 4-dimethylaminopyridine (193mg) in acetonitrile (10ml) under nitrogen. The
20 mixture was heated under reflux for 0.5h. More phosphorous oxychloride (ca 0.2ml) was added and the mixture was heated under reflux for a further 0.5h. The mixture was cooled to 22°C and allowed to stand for 18h, and poured onto triethylamine (6ml)/ice (6ml) with cooling. The aqueous phase was acidified to pH1 with conc hydrochloric acid, then extracted with ethyl acetate. The
25 combined organic extracts were washed with brine, dried (Na₂SO₄), and evaporated *in vacuo* to give a brown oil (1.3g) which was purified by chromatography over silica (Merck 9385, 30g). Elution with methanol:dichloromethane (2:98) gave the title compound as a beige foam (783mg).
30 TLC Silica (methanol:dichloromethane 2:98) R_f = 0.37.

Intermediate 20

(2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-(2,2,2-trifluoroethoxymethyl)-tetrahydro-furan-3,4-diol

- A solution of 6-chloro-9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purine (754mg) in trifluoroacetic acid (10ml) under nitrogen at -10°C was treated with water (1.0ml) and the mixture was stirred at -10°C to 0°C for 1.5h. The solvent was evaporated *in vacuo* at 20°C and the residue was treated with dichloromethane:ethanol:ammonia 10:8:1 (30ml) and the solvent removed *in vacuo* to give an oil. This was chromatographed on silica (30g). Eluting with methanol:dichloromethane (5:95) gave the title compound as a colourless foam (483mg, 71%).
- TLC Silica (methanol:dichloromethane 5:95) Rf = 0.26.

Intermediate 21

{2,2-Dimethyl-6R-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol

- A mixture of benzoic acid 3R,4R-bis-benzoyloxy-5R-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-2R-yl ester (8.25g), tetrahydro-pyran-4-ylamine hydrochloride (1.92g) and diisopropylethylamine (5.5ml) in isopropanol (100ml) was stirred under reflux, under nitrogen for 1.5h. The solution was concentrated *in vacuo* and the residue was treated with potassium carbonate (4.5g) in methanol (150ml). After 24h at 21°C more potassium carbonate (4.5g) was added and stirring was continued at 21°C for 64h. The solvent was evaporated *in vacuo* and the residue was absorbed on silica prior to purification by flash chromatography (250g), with dichloromethane:methanol:ammonia (90:10:1) eluant to give an off-white foam (3.7g). This material was dissolved in acetone (60ml) and treated with para-toluenesulphonic acid monohydrate (2.0g) and 2,2-dimethoxypropane (6ml) and the resulting mixture was stirred at 22°C overnight. The white suspension was concentrated *in vacuo* and the residue was partitioned between 8% aqueous sodium bicarbonate and ethyl acetate. The aqueous layer was further extracted with ethyl acetate and combined organic extracts were washed with water, brine, dried (Na₂SO₄) and concentrated *in vacuo* to a foam which was purified by flash chromatography over silica (100g) with ethyl acetate eluant to give the title compound as a colourless foam (3.49g). TLC Silica (ethyl acetate) Rf = 0.23

Intermediate 22

(9-{6R-[3-(tert-Butyl-dimethyl-silanyloxy)-propoxymethyl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-2-chloro-9H-purin-6-yl)-(tetrahydro-pyran-4-yl)-amine

Sodium hydride (60% dispersion in oil, 150mg) was added to a solution of tert-Butyl-(3-iodo-propoxy)-dimethyl-silane (720mg) in dry dimethylformamide (5ml) under nitrogen, and cooled in an ice-bath. After 1h the yellow mixture was treated with {2,2-Dimethyl-6R-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol (540mg) and stirred at room temperature for 17h. Acetic acid (0.5ml) was added and the mixture was stirred for 1h then poured into brine (15ml). The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were washed with water, brine, dried (Na₂SO₄) and concentrated *in vacuo* to a yellow oil. This sample was purified by flash chromatography on a silica column (5cm diam, toluene:ethanol:triethylamine, 95:5:1 eluant), repeated on a 3cm column, to give a pale yellow oil (269mg).
TLC Silica (toluene:ethanol:triethylamine 90:10:1) R_f = 0.39.

Intermediate 23

3-{6R-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethoxy}-propan-1-ol

A solution of (9-{6R-[3-(tert-butyl-dimethyl-silanyloxy)-propoxymethyl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-2-chloro-9H-purin-6-yl)-(tetrahydro-pyran-4-yl)-amine (420mg) in dry tetrahydrofuran (4ml) was treated with tetra-*n*-butylammonium fluoride (1M in tetrahydrofuran, 12ml) and the yellow solution was stirred at room temp for 3h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography over silica column (20g, toluene:ethanol:triethylamine 90:10:1 eluant) to give the title compound as a colourless gum (299mg).

TLC Silica (toluene:ethanol:triethylamine 90:10:1) R_f = 0.28

Intermediate 24

{2-Chloro-9-[6R-(3-fluoro-propoxymethyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine

A solution of 3-{6R-[2-Chloro-6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-ylmethoxy}-propan-1-ol

(280mg) in dichloromethane (3ml) was treated with diethylaminosulfur trifluoride (0.13ml) and the pale yellow solution was stirred at 22C for 17h. The reaction mixture was partitioned between ethyl acetate (10ml) and 2N sodium carbonate (10ml), the layers were separated and the aqueous layer was re-extracted with ethyl acetate (10ml). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated to a pale yellow oil which was purified by flash chromatography over silica (30g) eluting with toluene:ethanol:triethylamine (95:5:1) to give the title compound as an off-white foam (173mg). TLC Silica (toluene:ethanol:triethylamine 90:10:1) R_f = 0.41

Intermediate 25

9-[6R-(3-Fluoro-propoxymethyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl)-(tetrahydro-pyran-4-yl)-amine

A suspension of {2-chloro-9-[6R-(3-fluoro-propoxymethyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl)-(tetrahydro-pyran-4-yl)-amine (120mg), 5% palladium on carbon (50% aqueous paste, 180mg) and ammonium formate (120mg) in methanol (25ml) was stirred under reflux under nitrogen for 18h. The suspension was filtered through hyflo, evaporated *in vacuo* and the residue partitioned between ethyl acetate (5ml) and water (5ml). The aqueous layer was re-extracted with ethyl acetate (5ml) and the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to a semi-solid. The residue was treated with chloroform (~5ml) and the cloudy suspension was filtered through a cotton wool plug, and the filtrate concentrated *in vacuo* to give the title compound as a white foam (81mg). TLC Silica (toluene:ethanol:triethylamine 90:10:1) R_f = 0.33.

Example 1

N-(Tetrahydro-pyran-4-yl)-5'-O-trifluoromethyladenosine

Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (170mg), was heated under reflux with tetrahydro-pyran-4-ylamine hydrochloride (235mg) and diisopropylethylamine (0.35ml) in isopropanol (8ml) for 20h. After cooling, the solvent was removed *in vacuo* and saturated methanolic ammonia (15ml) added and the solution allowed to stand at 22°C for 3h. The solvent was evaporated *in vacuo* and the crude product

which was triturated with ether (6ml) to afford the title compound as a colourless powder (96mg).

Mass spectrum m/z 420 (MH^+)

Microanalysis Found: C, 45.7; H, 4.9; N, 16.3.

5 $C_{16}H_{20}F_3N_5O_5$ requires C, 45.8; H, 4.8; N, 16.7%.

Example 2

N-(2-Pyridin-4-yl-ethyl)-5'-O-trifluoromethyladenosine

10 (2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-trifluoromethoxymethyl-tetrahydro-furan-3,4-diol (42mg), 2-pyridin-4-yl-ethylamine (58mg), and diisopropylethylamine (0.124ml) were heated at 80°C in isopropanol (5ml) in a reactivial for 17h. The solution was evaporated under a stream of nitrogen and purified by autoprep HPLC to afford the title compound as a colourless solid (16mg).

15 Mass spectrum m/z 441 (MH^+)

HPLC R_t = 10.39 min.

Example 3

N-(exo-Bicyclo[2.2.1]hept-2-yl)-5'-O-trifluoromethyl-adenosine

20 Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (54mg), (\pm)-exo-norbonylamine (55mg) and diisopropylethylamine (0.128ml) were heated at 80° in isopropanol (7ml) in a reactivial for 65h. The solutions were blown down to small volume under a stream of nitrogen and saturated methanolic ammonia added and the solution
25 allowed to stand for 3h. The solution was evaporated *in vacuo* and the residue purified by chromatography using an SPE cartridge with chloroform then ethyl acetate-methanol (10:1) eluants to give the title compound as a colourless foam (51mg).

Mass spectrum m/z = 430 (MH^+)

30 LCMS R_t = 4.16 min.

Example 4

5'-O-Trifluoromethyladenosine

35 Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (53mg) was dissolved in saturated methanolic

ammonia (5ml) and allowed to stand at 22°C for 3 days. The sample was blown down under nitrogen and purified by flash chromatography over silica (10g) with dichloromethane-methanol (9:1) eluant to afford the title compound as a clear gum (8.3mg).

5 Mass spectrum $m/z = 336$ (MH^+)
LCMS Rt = 3.44 min.

Example 5

10 2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-ethanesulfonic acid methylamide

Acetic acid 4R-acetoxy-2R-(6-chloro-purin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (53mg) in isopropanol (5ml) was treated with (2-amino-ethanesulfonic acid methylamide) (85mg) and di-isopropylethylamine (0.211ml) and heated in a reactivial at 80°C for 65h. After cooling, the solvent was removed under a stream of nitrogen, and saturated methanolic ammonia added. The solution allowed to stand at 22°C for 3h, then treated with 8% sodium bicarbonate solution (5ml) and silica (5g), and the resulting mixture evaporated to dryness *in vacuo*. The resulting solid mixture was applied to a column of silica (20g) eluting with dichloromethane-methanol (20:1-5:1) to afford a colourless solid, which was recrystallised from methanol (2ml) to afford the title compound as colourless crystals (20mg).

20 Mass spectrum $m/z = 457$ (MH^+)
LCMS Rt = 3.62 min

25 Example 6

N-Cyclopentyl-5'-O-(2,2,2-trifluoro-ethyl)-adenosine

A solution of cyclopentyl-{9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-amine (100mg) in trifluoroacetic acid (2ml) at -10°C under nitrogen was treated with water (0.2ml) and the mixture stirred at -10° to 0°C for 4h. The solvent was evaporated *in vacuo* at 20°C and the residue treated with dichloromethane:ethanol:ammonia (10:8:1) and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography over silica (15g). Elution with dichloromethane:ethanol:ammonia (100:8:1) gave the title compound as a colourless solid (60mg) mp 74-6°C.

35

TLC Silica dichloromethane:ethanol:ammonia (100:8:1) R_f = 0.29

Mass spectrum m/z - 418 (MH^+)

Example 7

5 N-(Tetrahydro-pyran-4-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine

A solution of {9-[2,2-dimethyl-6R-(2,2,2-trifluoro-ethoxymethyl)-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine (90mg) in trifluoroacetic acid (2ml) under nitrogen at -10°C was treated with water (0.2ml) and the mixture stirred at -10°C to 0°C for 4h. The solvent
10 was evaporated *in vacuo*. The residue was purified by chromatography on silica at 20°C and the residue treated with dichloromethane:ethanol:ammonia (10:8:1) (15ml) and the solvent evaporated *in vacuo* (15g). Elution with dichloromethane:ethanol:ammonia (75:8:1) gave the title compound as a white solid (69mg) m.p. 80-2°C.

15 TLC Silica dichloromethane:ethanol:ammonia (75:8:1) R_f = 0.2

Example 8

N-(2R-Hydroxy-cyclopent-(R)-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine
(2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-(2,2,2-trifluoroethoxymethyl)-tetrahydro-
20 furan-3,4-diol (150mg) in isopropanol (5ml) under nitrogen was treated with (1R,2R)-2-amino-cyclopentanol (82mg), and diisopropylethylamine (0.28ml, 210mg), and heated under reflux for 18h. The solvent was evaporated *in vacuo* to give a residue which was purified by chromatography over silica (30g). Elution with dichloromethane:ethanol:ammonia (100:10:1) gave the title
25 compound as a beige solid (116mg) m.p. 164-6°.

TLC Silica (dichloromethane:ethanol:ammonia 100:10:1) R_f = 0.32

Example 9

N-(4-Fluoro-phenyl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine
30 (2R,3R,4S,5R)-2-(6-Chloro-purin-9-yl)-5-(2,2,2-trifluoroethoxymethyl)-tetrahydro-furan-3,4-diol (125mg) in isopropanol (5ml) under nitrogen was treated with 4-fluoroaniline (0.08ml, 90mg) and diisopropylethylamine (0.28ml, 210mg), and the mixture was heated under reflux for 24h. After cooling to 22°C the mixture was filtered, the filter cake washed with isopropanol (2ml) and ether (15ml) and

the solid dried *in vacuo* to give the title compound as a white solid (70mg), m.p. 214-5°.

TLC Silica (dichloromethane:ethanol:ammonia 100:10:1) R_f = 0.36

5 **Example 10**

5'-O-(3-Fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine

{9-[6R-(3-Fluoro-propoxymethyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(tetrahydro-pyran-4-yl)-amine (79mg) was dissolved in ice-cold trifluoroacetic acid (0.8ml), treated with water (0.08ml) then stirred at 0-5°C for 1h. The excess trifluoroacetic acid was removed under vacuum at 30°C, and the residue was purified by flash chromatography on a silica column (10g) with dichloromethane:methanol:ammonia (94:6:1) eluant to give the title compound as a colourless foam (52mg).

Mass spectrum *m/z* 412 (MH⁺)

15 TLC Silica (dichloromethane:methanol:ammonia 94:6:1) R_f = 0.14

Example 11

2-Chloro-5'-O-(3-fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine

A solution of {2-chloro-9-[6R-(3-fluoro-propoxymethyl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(tetrahydro-pyran-4-yl) amine (50mg) in trifluoroacetic acid (0.5ml) at 0°C was treated with water (0.05ml) and the reaction mixture was stirred at 0°C for 30 min. Excess trifluoroacetic acid was removed *in vacuo* at 30°C and the residue was purified by flash chromatography over silica (10g) with dichloromethane:methanol:ammonia (94:6:1) eluant to give the title compound as a colourless foam (32mg).

TLC Silica (dichloromethane:methanol:ammonia 94:6:1) R_f = 0.18

Mass spectrum *m/z* = 446 (MH⁺)

30 By analagous methods the following Examples were prepared:

Example 12 N-(2S-Fluoro-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 6

Mass spectrum *m/z* 422 (MH⁺)

35 HPLC R_t = 19.24min

Example 13 N-(Tetrahydro-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 6

Mass spectrum m/z 436 (MH^+)5 HPLC R_t = 17.61min**Example 14** N-(3,4-Difluoro-phenyl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 6

Mass spectrum m/z 448 (MH^+)10 HPLC R_t = 25.44min**Example 15** N-(3-Fluoro-phenyl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 6

Mass spectrum m/z 430 (MH^+)15 HPLC R_t = 24.65min**Example 16** N-(1,1-Dioxo-hexahydro-1. δ .6-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 5

20 LC/MS

 R_t = 3.62minMass spectrum m/z 468 (MH^+)**Example 17** N-tert-Butyl-5'-O-trifluoromethyl-adenosine

25 Prepared from Intermediate 5

LC/MS

 R_t = 4.12minMass spectrum m/z 392 (MH^+)**Example 18** 4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

Prepared from Intermediate 5

Mass spectrum m/z 491 (MH^+)35 Nmr δ ($CDCl_3$) 8.25 (1Hs, CH[heterocyclic]),

8.15(1Hs, CH[heterocyclic]), 6.05(1Hd, CH), 4.7 (1Hm, CH), 4.0-4.5 (9Hm, 5xCH + 2xCH₂), 3.1 (2H brt, CH₂), 2.08 (2H brd, 2xCH), 1.55 (2H brq, 2xCH), and 1.28 (3Ht, CH₃)

5 **Example 19** N-(2S-Hydroxy-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine
Prepared from Intermediate 5
LC/MS
R_t = 3.71min
Mass spectrum *m/z* 420 (MH⁺)

10 **Example 20** N-(rel-2,3-Dihydroxy-propyl)-5'-O-trifluoromethyl-adenosine
Prepared from Intermediate 5
LC/MS
R_t = 3.43min
15 Mass spectrum *m/z* 410 (MH⁺)

Example 21 N-(Tetrahydro-furan-3R-yl)-5'-O-trifluoromethyl-adenosine
Prepared from Intermediate 5
LC/MS
20 R_t = 3.62min
Mass spectrum *m/z* 406 (MH⁺)

Example 22 N-(Tetrahydro-furan-3S-yl)-5'-O-trifluoromethyl-adenosine
Prepared from Intermediate 5
25 LC/MS
R_t = 3.62min
Mass spectrum *m/z* 406 (MH⁺)

Example 23 N-{2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-ethyl}-acetamide
30 Prepared from Intermediate 5
LC/MS
R_t = 3.53min
Mass spectrum *m/z* 421 (MH⁺)

Example 24 4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-2-methyl-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester

Prepared from Intermediate 5

5

LC/MS

$R_t = 3.97\text{min}$

Mass spectrum m/z 505 (MH^+)

Example 25 2-Methyl N-(tetrahydro-pyran-4-yl)-5'-O-trifluoromethyl-adenosine

10

LC/MS

$R_t = 3.72\text{min}$

Mass spectrum m/z 434 (MH^+)

Example 26 N-(2-Chloro-4-fluoro-phenyl)-5'-O-trifluoromethyl-adenosine

15

Acetic acid 4R-acetoxy-2R-(6-chloropurin-9-yl)-5R-trifluoromethoxymethyl-tetrahydro-furan-3R-yl ester (0.16g), 2-chloro-4-fluoroaniline (0.26ml), palladium acetate (8mg), R-BINAP (R-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl) (33mg) and cesium carbonate (0.16g) in 1.2ml of toluene were heated in a reactivial at 85-91°C for 16h. The reaction mixture was cooled to room temperature and quenched with water (20ml) and extracted with dichloromethane (3x50ml). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The resulting residue was purified by flash chromatography over silica (8g Biotage column) eluting with cyclohexane-ethyl acetate 9:1-6:4) to give a clear oil which was dissolved in 1ml of methanol, cooled to 0-5°C and treated with t-butylamine (0.05ml). The mixture was kept at this temperature for 1h and evaporated to dryness *in vacuo* to give the title compound (67mg) as a white solid.

20

25

LC/MS

30

$R_t = 3.04\text{min}$

Mass spectrum m/z 464 (MH^+), 466 ($MH^+ + 2$)

Example 27 N-(4-Chloro-2-fluoro-phenyl)-5'-O-trifluoromethyl-adenosine

Prepared from Intermediate 5 by analogous method to Example 26.

35

LC/MS

42

$R_t = 3.16\text{min}$

Mass spectrum m/z 464 (MH^+), 466 ($\text{MH}^+ + 2$)

Reporter Gene Experiments

Agonist activity was measured in Chinese hamster ovary (CHO) cells containing the CRE/SPAP/HYG (CRE = cyclic AMP response element; HYG = hygromycin resistance; SPAP = secreted placental alkaline phosphatase) reporter gene elements, which upon stimulation of cAMP levels produced SPAP. A cell line was used, which was stably transfected with either the human adenosine A1 receptor or the human adenosine A3 receptor in addition to the above elements. Cells were plated out in 96-well plates in culture medium and incubated at 37°C for 1 hour. For measurement of potency, agonists were added to the appropriate wells at a concentration range of approximately 10^{-10} - 10^{-5} M. 15Min later, cAMP levels were stimulated by addition of a maximal concentration of forskolin. All cells were then incubated for a further 5 hours at 37°C, and cooled to room temperature, after which a substrate for the phosphatase (para-nitrophenol phosphate, pNPP), which is converted by SPAP to a coloured reagent) was then added and the 96-well plates were read in a plate reader. From these readings, the concentration-dependence of the inhibition by the agonist for forskolin-stimulated SPAP production can be calculated. One of the agonists tested on each 96-well plate was the standard non-selective agonist, N-ethylcarboxamidoadenosine (NECA), and the potency of all test agonists is expressed relative to that of the NECA standard.

(ECR = equipotent concentration ratio relative to NECA = 1)

Results

Table 1
Biological Data. A1, A3 Receptor, Receptor Gene Assay ECR

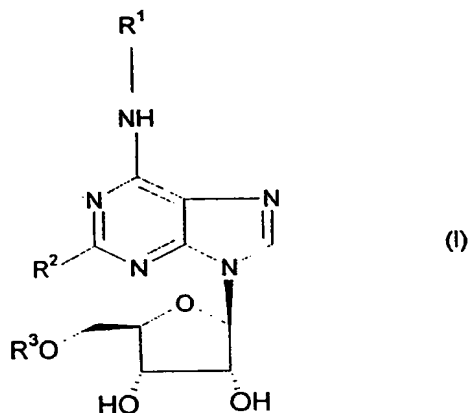
5

| Example | A1 | A3 |
|----------------|-----------|-----------|
| 1 | 8.40 | >129 |
| 2 | 185.5 | - |
| 3 | 5.60 | 143.5 |
| 4 | 80.7 | 81.6 |
| 5 | 33.2 | >212 |
| 6 | 8.70 | 7.7 |
| 7 | - | - |
| 8 | 239.40 | - |
| 9 | 298 | 19.7 |
| 10 | - | - |
| 11 | - | - |
| 12 | 1.87 | >226 |
| 13 | 11.1 | >276 |
| 14 | 20.50 | 197.3 |
| 15 | 23.2 | - |
| 16 | 79.50 | >207 |
| 17 | 138.8 | >207 |
| 18 | 5.32 | >202 |
| 19 | 12.10 | >150 |
| 20 | 24.10 | 284.5 |
| 21 | 10.90 | >175 |
| 22 | 10.40 | >63 |
| 23 | 12.52 | >175 |
| 24 | 51.70 | >134 |
| 25 | 32 | - |

45

Claims

1. A compound of formula (I)



wherein R^2 represents C_{1-3} alkyl, halogen or hydrogen;

R^3 represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms;

R^1 represents a group selected from

- (1) $-(alk)_n-$ (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, $-(C_{1-3})$ alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.
- (2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S optionally substituted by one or more substituents selected from the group consisting of $-(C_{1-3})$ alkyl, $-CO_2-(C_{1-4})$ alkyl, $-CO(C_{1-3})$ alkyl, $-S(=O)_n-(C_{1-3})$ alkyl, $-CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3} alkyl) or $=O$; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

- (3) Straight or branched C₁₋₁₂ alkyl, optionally including one or more O, S(=O)_n (where n is 0, 1 or 2), or N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy or NR^aR^b wherein R^a and R^b both represent C₁₋₃alkyl or hydrogen.
- (4) a fused bicyclic aromatic ring



wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted -CO₂-(C₁₋₃alkyl).

- (5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, -SO₃H, -(alk)_nOH^c, -(alk)_n-cyano, -(O)_n-(C₁₋₆)-alkyl (optionally substituted by one or more halogens), -(alk)_n-nitro, -(O)_m-(alk)_n-CO₂R^c, -(alk)_n-CONR^cR^d, -(alk)_nOR^c, -(alk)_n-COR^c, -(alk)_n-SOR^e, -(alk)_n-SO₂R^e, -(alk)_n-SO₂NR^cR^d, -(alk)_nOR^c, -(alk)_n-(CO)_m-NHSO₂R^e, -(alk)_n-NHCOR^c, -(alk)_n-NR^cR^d wherein m and n are 0 or 1 and alk represents a C₁₋₆alkylene group or C₂₋₆ alkenyl group.

- (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C₁₋₃alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C₁₋₃ alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms which heterocyclic ring may optionally be substituted further by one or more C₁₋₃ alkyl groups.

R^e represents C₁₋₃alkyl.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

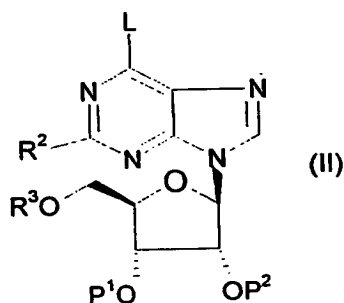
- 5 2. A compound according to claim 1 wherein R³ represents a C₁₋₃ fluoroalkyl group.
3. A compound according to claim 2 wherein R³ represents a fluoromethyl group.
4. A compound according to claim 1 wherein R³ represents trifluoromethyl group.
- 10 5. A compound according to any of claims 1-4 wherein R² represents hydrogen, methyl or halogen.
6. A compound according to claim 5 wherein R² represents hydrogen, methyl or chlorine.
- 15 7. A compound according to any of claims 1-6 wherein R¹ represents (alk)_n - C₃₋₆ - cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen or OH or is unsubstituted.
8. A compound according to claim 7 wherein n represents zero.
9. A compound according to claim 8 wherein the cycloalkyl is
- 20 10. A compound according to any of claims 7-9 wherein the cycloalkyl ring has 5 carbon members.
11. A compound according to any of claims 1-6 wherein R¹ represents a
- 25 substituted or unsubstituted aliphatic heterocyclic group, the substituent being selected from the group consisting of -(CO₂) -(C₁₋₄) alkyl -CO-(C₁₋₃)alkyl, -S(=O)_n-(C₁₋₃)alkyl, CONR^aR^b wherein R^a and R^b are defined

herein above, and when there is a heteroatom S in the ring, this heteroatom may optionally be substituted by $(=O)_n$ where n is 0, 1 or 2.

- 5 12. A compound according to claim 12 wherein the heterocyclic ring is unsubstituted or the substituents are $-\text{CO}_2(\text{C}_{1-4})\text{alkyl}$, or when the heteroatom is S, the substituent $(=O)_n$ is attached to the heterocyclic S atom. More preferably, when there is a sulfur heteroatom in the ring this S is unsubstituted.
13. A compound according to claim 12 where in the sulfur heteroatom is unsubstituted.
- 10 14. A compound according to claim 11 wherein the aliphatic heterocyclic group is unsubstituted or when the substituent is $-\text{CO}_2(\text{C}_{1-4})\text{alkyl}$, the heteroatom is N and the substituent is attached directly to the ring N atom.
- 15 15. A compound according to any of claims 11-15 wherein the heterocyclic ring is 5 or 6 membered and more preferably contains any one O, N or S heteroatom.
16. A compound according to any of claims 1-6 wherein R^1 represents a straight or branched alkyl of 1-5 carbon atoms optionally with at least one $\text{S}(=O)_n$ where n is 0, 1 and/or N substituted in the chain.
- 20 17. A compound according to claim 16 wherein when there is $\text{S}(=O)_n$ in the chain n is 1 or 2.
18. A compound according to claims 15-17 wherein the alkyl group may be unsubstituted or substituted by at least one OH group.
- 25 19. A compound according to any of claims 1-6 wherein R^1 represents a phenyl group substituted by one or more substituents selected from OH and halogen.
20. A compound according to claim 19 wherein the phenyl group is disubstituted in the 2, 4 positions.
21. A compound according to claim 20 wherein both substituents are halogen.

22. A compound according to claim 21 wherein the 2 substituents is fluoro and the 4-substituent is chloro.
23. A compound according to claim which is
- 5 N-(Tetrahydro-pyran-4-yl)-5'-O-trifluoromethyl-adenosine,
N-(2-Pyridin-4-yl-ethyl)-5'-O-trifluoromethyl-adenosine,
N-(2S-Fluoro-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine,
N-(Tetrahydro-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine,
N-(3,4-Difluoro-phenyl)-5'-O-trifluoromethyl-adenosine,
N-(3-Fluoro-phenyl)-5'-O-trifluoromethyl-adenosine,
10 N-(exo-Bicyclo[2.2.1]hept-2-yl)-5'-O-trifluoromethyl-adenosine,
N-(1,1-Dioxo-hexahydro-1. δ .6-thiopyran-4-yl)-5'-O-trifluoromethyl-adenosine,
N-tert-Butyl-5'-O-trifluoromethyl-adenosine,
4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-
15 9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,
N-(2S-Hydroxy-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine,
N-(rel-2,3-Dihydroxy-propyl)-5'-O-trifluoromethyl-adenosine,
N-(Tetrahydro-furan-3R-yl)-5'-O-trifluoromethyl-adenosine,
N-(Tetrahydro-furan-3S-yl)-5'-O-trifluoromethyl-adenosine,
20 N-{2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-9H-purin-6-ylamino]-ethyl}-acetamide,
5'-O-Trifluoromethyl-adenosine,
2-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-
9H-purin-6-ylamino]-ethanesulfonic acid methylamide,
25 4-[9-(3R,4S-Dihydroxy-5R-trifluoromethoxymethyl-tetrahydro-furan-2R-yl)-2-methyl-9H-purin-6-ylamino]-piperidine-1-carboxylic acid ethyl ester,
2-methyl N-(tetrahydro-pyran-4-yl)-5'-O-trifluoromethyl-adenosine,
5'-O-(3-Fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine,
2-Chloro-5'-O-(3-fluoro-propyl)-N-(tetrahydro-pyran-4-yl)-adenosine,
30 N-Cyclopentyl-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
N-(Tetrahydro-pyran-4-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
N-(2R-Hydroxy-cyclopent-(R)-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine,
N-(4-Fluoro-phenyl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine.

24. A compound according to any previous claim which has little or no activity at the A3 receptor.
25. A compound according to any of claims 1-24 for use in therapy.
26. A pharmaceutical composition comprising a compound according to any of claims 1-24 together with a pharmaceutical carrier and/or excipient.
27. Use of a compound according to any of claims 1-24 for the manufacture of a medicament for the treatment of a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea.
28. A method of treating a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea, comprising administering a therapeutically effective amount of a compound according to any of claims 1-24.
29. A method for preparing a compound according to claim 1 which by reaction of a compound of formula (II)



51

wherein L represents a leaving group and P¹ and P² represent hydrogen or a suitable protecting group and R¹, R² and R³ are as defined in claim 1 with a compound R¹ NH₂ or salt thereof under basic conditions.

5

THIS PAGE RI ANK (ISPTO)

INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/EP 98/07022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/16 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 97 33591 A (NOVONORDISK AS) 18 September 1997 see page 17, line 1 - line 5; claims 1,7-10 | 1,24-29 |
| A | WO 95 28160 A (RHONE-POULENC RORER PHARMA ; SPADA ALFRED P (US); FINK CYNTHIA A (U) 26 October 1995 see page 11, line 10 - page 12, line 25 | 1,24-29 |
| P,A | WO 97 43300 A (GLAXO GROUP LTD ; ELLIS FRANK (GB); SWANSON STEPHEN (GB); COUSINS R) 20 November 1997 see claim 1; table 2 | 1,24-29 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 June 1999

Date of mailing of the international search report

18/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/ 07022

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 28
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No

PCT/EP 98/07022

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9733591 A | 18-09-1997 | AU 2022497 A | 01-10-1997 |
| | | AU 2022597 A | 01-10-1997 |
| | | WO 9733590 A | 18-09-1997 |
| WO 9528160 A | 26-10-1995 | US 5561134 A | 01-10-1996 |
| | | AU 684635 B | 18-12-1997 |
| | | AU 2294995 A | 10-11-1995 |
| | | BG 100963 A | 29-08-1997 |
| | | BR 9507327 A | 07-10-1997 |
| | | CA 2188147 A | 26-10-1995 |
| | | CN 1148811 A | 30-04-1997 |
| | | CZ 9603032 A | 14-05-1997 |
| | | EP 0758897 A | 26-02-1997 |
| | | FI 964218 A | 17-12-1996 |
| | | HU 75331 A | 28-05-1997 |
| | | JP 9512020 T | 02-12-1997 |
| | | NO 964438 A | 18-10-1996 |
| | | PL 316961 A | 17-02-1997 |
| | | SI 9520055 A | 30-06-1997 |
| | | SK 134096 A | 07-05-1996 |
| | | US 5736554 A | 07-04-1998 |
| | | US 5652366 A | 29-07-1997 |
| WO 9743300 A | 20-11-1997 | AU 2896197 A | 05-12-1997 |
| | | EP 0901499 A | 17-03-1999 |

THIS PAGE BLANK (USPTO)

App. No. 10/608,689
Filed: June 27, 2003
Inventor: BIGOT, et al.
Docket No. DEAV2002/0059 US NP
PRIOR ART

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)